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INTEGRATIVE REVIEW OF THE LITERATURE

Treatment of child with phenylketonuria: a literature review

Triagem neonatal e tratamento de criança com fenilcetonúria: uma revisão integrativa da literatura

Tratamiento del niño con fenilcetonuria: una revisión de la literatura

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ABSTRACT

Objective: To analyze the importance of Neonatal Screening for the treatment of children with phenylketonuria. **Method:** This is an integrative review. To select the studies we looked at the electronic databases Scientific Electronic Library Online - SciELO journal portal and CAPES in September 2013, using the keywords: Phenylketonuria, Triage, Child health. **Results**: The analysis of the articles indicated that in the period 2008-2013, the year 2010 had the highest number of publications. Most studies paused to examine the importance of neonatal screening program to evaluate the tracking phenylketonuria, as well as to characterize the performance of children diagnosed and treated early with phenylketonuria. **Conclusion:** Studies have shown that treatment is significantly more effective when deployed in pre - clinical stage of the disease and there is a screening test, the screening test, which is simple, efficient , applicable on a large scale and low cost. **Descriptors:** Phenylketonuria, Triage, Child health.

RESUMO

Objetivo: Analisar a importância da Triagem Neonatal para o tratamento de crianças com fenilcetonúria. **Método:** Trata-se de uma revisão integrativa. Para selecionar os estudos, pesquisou-se nas bases de dados eletrônicas Scientific Eletronic Library Online – SCIELO e Portal de Periódicos da CAPES em setembro de 2013, utilizando os descritores: fenilcetonúria, triagem e saúde da criança. **Resultados**: A análise dos artigos indicou que no período de 2008 a 2013, o ano de 2010 teve o maior número de publicações. A maioria dos estudos deteve-se em analisar a importância da triagem neonatal, avaliar o programa para rastreamento de fenilcetonúria, assim como caracterizar o desempenho de crianças com fenilcetonúria diagnosticadas e tratadas precocemente. **Conclusão**: Os estudos mostraram que o tratamento é significativamente mais eficaz quando implantado na fase pré-clínica da doença e existe um teste de triagem, o teste do pezinho, que é simples, eficiente, aplicável em larga escala e de baixo custo. **Descritores:** Fenilcetonúria, Triagem e Saúde da criança.

RESUMEN

Objetivo: Analizar la importancia de Tamizaje Neonatal para el tratamiento de los niños con fenilcetonuria. **Método:** Se trata de una revisión integradora. Para seleccionar los estudios que analizamos las bases de datos electrónicas Scientific Electronic Library Online - Portal de la revista SciELO y CAPES en septiembre de 2013, utilizando las palabras clave: Fenilcetonuria, Triaje, Salud del Niño. **Resultados:** El análisis de los artículos se indica que en el período 2008-2013, el año 2010 tuvo el mayor número de publicaciones. La mayoría de los estudios se detuvieron para examinar la importancia del programa de cribado neonatal para evaluar los fenilcetonuria seguimiento, así como para caracterizar el rendimiento de los niños son diagnosticados a tiempo con fenilcetonuria. **Conclusión:** Los estudios han demostrado que el tratamiento es significativamente más eficaz cuando se despliega en la etapa de pre - clínica de la enfermedad y hay una prueba de detección, la prueba de detección, que es simple, eficaz, aplicable a gran escala y bajo costo. **Descriptores:** Fenilcetonuria, Triaje, Salud del niño.

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INTRODUCTION

Phenylketonuria (PKU) is the most common of the inborn errors of amino acid metabolism. Due to a deficiency of phenylalanine hydroxylase, the enzyme that catalyzes the conversion of phenylalanine to tyrosine. The introduction of a diet low in phenylalanine should begin in the first months of life, preferably in the first month, to prevent mental retardation and more severe manifestation of the disease.[1]

The hyperphenylalaninemia (HPA), the generic name given to high levels of phenylalanine (Phe) in blood, is a primary disorder of hydroxylating Phe system, which may be caused by a deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH) or enzymes that synthesize or reduce the tetrahydrobiopterin coenzyme.[2]

Phenylalanine is an essential aromatic amino acid, mainly metabolised in the liver. Phenylalanine which is not required for protein anabolism, tyrosine is hydroxylated by phenylalanine hydroxylase. This has a quaternary structure having four polypeptide chains, each connected to an iron atom, that binds oxygen, to form tyrosine.[3]

Different types of hyperphenylalaninemia can be found, according to the metabolic error involved, forming a heterogeneous group of diseases, including phenylketonuria (PKU) and classical variations of hyperphenylalaninemia (PAHs), as persistent HPA, the mild HPA and atypical PKU.[4]

Currently in the healthcare scenario phenylketonuria has been diagnosed through neonatal screening tests, popularly known as the Guthrie Test, which is mandatory throughout the country since the 80s, after the implementation of the National Neonatal Screening Program (NNSP). Thus, all newborns should undergo this test for screening of some metabolic abnormalities, including phenylketonuria, targeting the immediate initiation of treatment.[5,6]

The phenylketonuric subjects are clinically normal at birth, beginning to manifest developmental delays around 6 months of age, with spasms, hypotonia, and rash. Display reduced pigmentation, microcephaly and epilepsy. The excretion of phenylketones provides the urine the characteristic odor.[7]

However, it is known that Brazil is ethnically, socially and economically marked by numerous inequalities, making difficult the establishment and development of health programs, as an example of Neonatal Screening for the treatment of phenylketonuria. Thus, the success and effectiveness of neonatal screening programs depend mainly on the involvement of health authorities, educational campaigns including healthcare professionals and the population and investments.

Given this issue the study aims to analyze the importance of Neonatal Screening for the treatment of children with phenylketonuria.

METHODOLOGY

This study is an integrative review. For its construction the following steps were covered: establishment of hypothesis and objectives of the integrative review, establishment of criteria for inclusion and exclusion of articles (sample selection); definition of information to be extracted from the selected articles, analysis of results, discussion and presentation the results and the last stage consisted of submitting the review.[8]

The guiding question for the construction of this integrative review was "What is the importance of Neonatal Screening for the treatment of phenylketonuria?". To select the references we looked at the electronic databases Scientific Electronic Library Online - SciELO and Periodical Portal CAPES in September 2013.

In search for articles by standardized Descriptors in Health Sciences Headings (DECs) were to be used descriptors, which were: Child and neonatal phenylketonuria.

After application of the descriptors the following results were found: in the database SCIELO sixty-six (26) Articles and Portal CAPES center and eighty (180) articles. The articles were subjected to cuts, which may be below Viewed in figure 1.

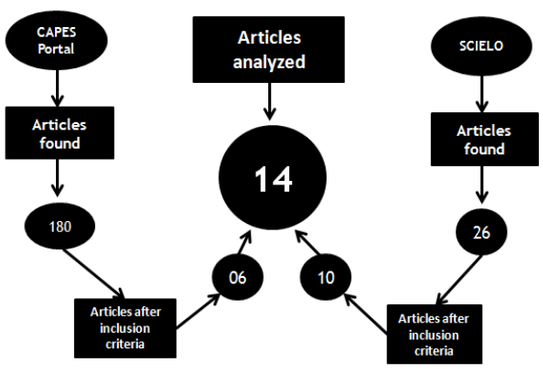

Figure 1: search the banks of SCIELO and CAPES Portal Data Strategy. Teresina, 2013

Following the electronic search, in order to identify items considered relevant and exclude those who did not meet the inclusion criteria, were selected survey regarding guiding question, full text, with humans (children), with reference to treatment of children with phenylketonuria and published since 2008.

After identifying the related study material sorting the items, by reading the titles and abstracts was performed. Being excluded from jobs as editorials, thesis, dissertations, book reviews and interviews. After this step remained for the final sample of this review 14 articles. Studies that met the inclusion criteria were obtained in full.

For the final analysis of the study an instrument that includes the following items was prepared: identifying the original article, methodological characteristics of the study, assessment of the methodological rigor of interventions measured and the results. In the next step, the data were subjected to critical analysis and further discussion and description of the results.

RESULTS AND DISCUSSION

Frame 1 presents data on the articles analyzed for year, database, the publication title and magazines. The results indicated that 14 articles were published in the period 2008-2013, with the year 2010 a large number of publications with four, followed by 2009 and 2012 with three two respectively. Have 2011 and 2013 had two publications each year. In reference to thematic of 2008 showed up with smaller publication, highlighting just one article.

Regarding indexing of publications related to the theme was highlight the database SCIELO with nine published articles, followed by CAPES Portal with five. The more related to disclosures of research journal was the Brazilian Metabolic Endocrinology file with three articles and the rest were distributed in different journals that are synoptically highlighted in the table below.

Frame 1 - Details of the articles analyzed according to the database, year of publication, title of the article and periodicals of the publication. Teresina (PI), 2013.

Order of the Articles	Database	Year of publication	Title of the article	Periodicals of the publication
A1	P. CAPES	2008	Neonatal screening: what pediatricians should know	Journal of Pediatrics
A2	P. CAPES	2009	Newborn Screening Program, Hospital das Clinicas, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Brazil	Reports in public health
A3	SCIELO	2009	Metabolism of calcium in phenylketonuria	Brazilian Journal of Nutrition
A4	SCIELO	2009	Evaluation of Reference Service for Neonatal Screening for congenital hypothyroidism and phenylketonuria in Mato Grosso, Brazil.	Brazilian Archives of Endocrinology & Metabolism
A5	SCIELO	2010	Audiological findings in children with phenylketonuria.	Revista da Sociedade Brasileira de Fonoaudiologia
A6	SCIELO	2010	Child development in phenylketonuria: speech therapy.	Revista CEFAC
A7	SCIELO	2010	Performance of children with phenylketonuria in the Denver Development Screening Test - II.	Pró-Fono Revista de Atualização Científica
A8	P. CAPES	2010	Newborn screening - the challenge of universal and effective coverage	Ciencia & Saude Coletiva
A9	P. CAPES	2011	Performance Analysis of Newborn Screening Program in the State of Rio de Janeiro, Brazil, 2005-2007	Reports in Public Health
A10	SCIELO	2011	Clinical and demographic aspects of phenylketonuria in the State of Bahia	Journal of Pediatrics
A11	P. CAPES	2012	Phenylketonuria, congenital hypothyroidism and hemoglobinopathies: public health issues for a program of neonatal screening Brazilian	Reports in Public Health
A12	SCIELO	2012	Nutritional status and ingestion of selenium in children with phenylketonuria in Minas Gerais, Brazil	Journal of Pediatrics
A13	SCIELO	2013	Prevalence of pathologies detected by newborn screening in Santa Catarina	Brazilian Archives of Endocrinology & Metabolism
A14	SCIELO	2013	Evolution of the neonatal screening program in the state of Tocantins	Brazilian Archives of Endocrinology & Metabolism

Source: Direct, Search 2013. Legend: A-Article, E-Portal.

Frame 2 is envisioned that the studies stopped to check the importance of screening of children diagnosed with PKU, the clinical and epidemiological characteristics, treatment, causes, demographic characteristics and clinical findings. Thus, the main objectives were related to: verify the importance of newborn screening for metabolic disorders and to evaluate the preventive and health promotion of children with phenylketonuria actions, analyze the causes, symptoms and dietary treatment of PKU infants; assess the national and international prevalence of phenylketonuria; characterize the performance, clinical and demographic characteristics of children with phenylketonuria.

Frame 2 - Details of the articles analyzed in accordance with objectives of the studies. Teresina (PI), 2013.

Order of Articles	STUDIES OBJECTIVES
A1	Evaluate the state of newborn screening in the world and in Brazil. Define the role of pediatricians in neonatal screening programs.
A2	Evaluate the Newborn Screening Program, Hospital das Clinicas, Faculty of Medicine of Ribeirão Preto from 1994 to 2005, mainly on the range of coverage, the time elapsed between birth and time of the examination, the examination arrival to the laboratory and release of results as well as the children's ages at the onset of treatment.
A3	Understanding the need of calcium supplementation for children with phenylketonuria, in order to promote proper bone mineralization.
A4	Evaluate the Reference Service for Neonatal Screening for congenital hypothyroidism and phenylketonuria in the State of Mato Grosso.
A5	To investigate changes in hearing of children with phenylketonuria diagnosed and treated early and compare the results with those found in the auditory evaluation of normal children of the same age.
A6	Show developmental disorders observed in scientific studies with individuals with phenylketonuria and reflect upon skills related to language development.
A7	Characterize the performance of children with phenylketonuria diagnosed and treated early through the Denver II Screening Test Development and blood levels of phenylalanine.
A8	Make a more extensive search possible on the status of NSP coverage in several regions in the world, as well as issues concerning the time of collection, seeking to draw a parallel between the situation of the Brazilian program and its equivalents in other countries.
A9	Analyze performance in achieving the common goals such as coverage and effectiveness of the steps of collecting the diagnostic confirmation, contrasting strategies used in each step for each model.
A10	Describe the clinical and demographic characteristics of patients with hyperphenylalaninemia accompanied the Reference Service for Neonatal Screening of Bahia.
A11	To analyze the frequency of detection of congenital hypothyroidism, phenylketonuria and hemoglobinopathies in Newborn Screening Program of the State of Rio de Janeiro, Brazil, between 2005 and 2007.
A12	Estimate dietary intake and nutritional status in selenium in patients with phenylketonuria.
A13	To evaluate the prevalence of diseases phenylketonuria (FNC), congenital hypothyroidism (CH), cystic fibrosis (CF), hemoglobin (HB) and congenital adrenal hyperplasia (CAH) in the State of Santa Catarina, in order to outline the profile of the population in Santa Catarina in relation to these pathologies.
A14	Evaluate the Newborn Screening Program in the State of Tocantins 1995-2011.

Source: Direct, Search 2013. Legend: A-Article, E-Portal.

In reference to the results of the studies can be inferred that the same reported various aspects of the importance of newborn screening, referring to the main consequences brought about by the condition and the effectiveness of the screening program to treat the disease, among other relations presented in frame 3.

Frame 3 - Details of articles analyzed according to the authors and the principal considerations identified in the studies. Teresina (PI), 2013.

Order of articles	AUTHORS	PRINCIPAL CONSIDERATIONS
A1	Leão LL; Aguiar MJB	In Brazil, the National Newborn Screening Program was set up in 2001, against screening for phenylketonuria, congenital hypothyroidism, sickle cell anemia and cystic fibrosis.
A2	Magalhães PKR; Turcato MF; Angulo IL et al.	The Hospital of the Faculty of Medicine of Ribeirao Preto - HCFMRP established in 1994 has already diagnosed by 2005, 76 children with congenital hypothyroidism, phenylketonuria and 10 to 25 with hemoglobinopathies.
A3	Martins FF; Mendes AB; Cruz WMS et al.	The diet as a strategy for reducing the levels of phenylalanine in the blood of patients with phenylketonuria, if not followed, then leads to long-term problems in bone formation.
A4	Stranieri I; Takano OA	Of total screening tests in Reference Service for Newborn Screening for congenital hypothyroidism and phenylketonuria in the State of Mato Grosso, stands out a population coverage below 70%.
A5	Mancini PC; Starling ALP; Penna LM; Ramos CAV et al.	In the group with phenylketonuria, 66.7% of children had normal hearing and 33.3% with conductive hearing loss.
A6	Lamonica DAC; Gejão MG; Ferreira AT et al.	Individuals with phenylketonuria, even treated early, may show changes in cognitive, language, motor and social-behavioral functions.
A7	Silva GK; Lamonica DAC	Children with phenylketonuria diagnosed and treated early showed deficits in personal-social and language areas.
A8	Camacho JB; Bastos LA; Cruz MM et al.	The results of the study showed that Canada had coverage of 71% in 2006. The European coverage was 69% in 2004, with data from 38 countries. In Asia and the Pacific, there was data from nineteen countries. Middle East and North Africa, there were data from four countries. In Latin America, coverage was 49% in 2005, with data from fourteen countries. In Brazil, the coverage was 80% in 2005.
A9	Botler J; Camacho LAB; Cruz MM	In performance analysis of NSP from 2005 to 2007, coverage was increased and reached 80.4%, with 33.8% of collections made within 7 days.
A10	Amorim T; Boa-Sorte N; Leite MEQ et al.	The incidence of hyperphenylalaninemia in Bahia was one case per 16,334 live births, with coverage of 91%. Among the patients, 82% were diagnosed by neonatal screening, and 11 families had more than one case.
A11	Botler J; Camacho LAB; Cruz MM.	In 2007, coverage of the Newborn Screening Program of the State of Rio de Janeiro has reached 80.7%. The increase in the incidence of congenital hypothyroidism (1:1.030 in 2007) was attributed to the decrease in TSH cutoff value over time.
A12	Alves MKA; Starling ALP; Kanufre VC et al.	The average time of supplementation of selenium, in particular formula, was 122.2 ± 25.1 days. The amino acid mixture supplemented with mineral represented 72.9% of the daily supply of selenium.
A13	Nunes AKC; Wachholz RG; Rover MRM et al.	The coverage of the program in the period analyzed scores a 90%, so the prevalence of pathologies derived from the screened population can be extrapolated to the prevalence found in the entire population of Santa Catarina.
A14	Mendes LC; Santos TT; Bringel FA.	Coverage of neonatal screening increased from 32.3% to 76.6% after implementation of the National Newborn Screening Program.

Source: Direct, Search 2013. Legend: A-Article

After analysis it was realized that Brazil has a Newborn Screening Program that follows international guidelines, which appears to be irreversible, since it represents a considerable technical advance, being known worldwide as the largest public health program linked to genetics.

But its consolidation is subject to certain medical and ethical issues that need to be discussed, because the progress of the program are new challenges as new issues and diseases are introduced into the diseases screened panel.[9]

But to the Newborn Screening Program can fully achieve its objectives, it is essential that some goals are met, as: collection of the blood

sample obtained properly and in adequate time; fast referral of sample to the reference laboratory, conduct of examinations by laboratory obeying strict quality control, quick communication of test results; reference center endowed with doctor (s) trained (s) to establish (in) accurate diagnosis and structure for clinical follow-up of affected children; periodic evaluations of the quality program, reporting their results to the authorities, so that any improvements can be implemented. [10]

Thus, is emphatic to highlight that the process of newborn screening is not limited to collecting material for analysis, but is secondary to this, because without the dialogue with the other aforementioned steps, the program is limited and its proposal for early screening for the actual outcome / treatment and prevention of sequelae for child development become ineffective.[11]

Furthermore, within your functioning healthcare team involved has a role of great value, especially pediatricians and speech therapists occupy an important position in the treatment, the possible changes in referrals and improving the quality of life of these children, however data show that scientific knowledge pediatrician about the diseases screened, treatment and prognosis is still not concrete hampering the progress and establishment of some program issues, as well as effective treatment of children with phenylketonuria through diagnostic screening.[9,12]

Nationwide access to newborn screening is very heterogeneous, for example, in 2007 in the state of Rio de Janeiro coverage reached 80.7%, unlike other cities. [13,14]

Thus, states with less government involvement have a lower coverage, and those who have a position where the respective administrative bodies are more active, have greater coverage. Therefore, the involvement of health, government and local authorities and professional societies are critical milestones, not

only for the scope of coverage, but also with respect to the degree of opportunity of the collections.[11]

In this perspective it is important to emphasize that the Newborn Screening Program continually goes through reviews should meet the minimum requirements recommended by the Ministry of Health in the state of Tocantins, for example, the data indicate a significant evolution of the coverage rate, showing that the prevalence of diseases such as phenylketonuria and congenital hypothyroidism possessed lower rate than the national average, in turn, in Santa Catarina phenylketonuria was lower than the national prevalence, while the second condition was similar to global and national values.[15,16]

Also according to program evaluations collection of the first blood sample and initiation of treatment in many cases still occurs at a higher time than recommended by the Ministry of Health and delays that accumulate in various stages of the screening process can nullify the benefits of early detection, precept of a neonatal screening program. [14] Despite this evidence in literature suggests a positive perception of parents about the deployment, quality and evolution of the Newborn Screening Program, but there is controversy about the need for greater government support for such a program is optimized and can advance to the next stages.[16]

In this regard it is worth noting that the Newborn Screening Program is critical both for early screening of diseases that previously were not known, especially PKU, but mainly for the improvement and reduction in infant mortality from other diseases of genetic imprint.

But the early screening of diseases such as phenylketonuria achieved by the program does not guarantee a cure, as an example, it is important to highlight that individuals with phenylketonuria, even with early treatment, may show changes in cognitive functions, language, motor and social-behavioral. Thus scientific findings justify the referral of new proposals to the Ministry of Health with a view to hiring Speech Therapists in Newborn Screening Programs credentialed for full monitoring of individuals with this condition, ensuring less commitment and more effective treatment.[17]

Moreover, even with treatment and appropriate follow-up is still physiological changes caused primarily by dietary treatment, resulting from the disability and severe restriction on the consumption of foods containing the amino acid phenylalanine and secondary to this, other nutrients. This results in low intake of several nutrients, including selenium and calcium. Even with supplementation with formulas that seek to meet the needs of vitamins, minerals and essential amino acids, nutritional deficiencies are not discarded.[18,19]

However, scientific evidence showed that dietary treatment did not influence physiological changes in children with phenylketonuria, with an emphasis on auditory changes. Thus more studies showing the relationship of certain mixtures to recover possible deficiencies found and to ensure treatment and quality of life more suited to patients with phenylketonuria is needed.[12]

It is unquestionable that the Newborn Screening Program is extremely relevant for screening and early treatment of children diagnosed with PKU, however is noticeable through the scientific literature that changes accompanying the life cycle of these individuals, especially in the personal-social interaction, language and fine motor adaptive. In this sense, its long development is marked by changes that continually undermine your communication, social integration and learning.[20]

Thus the strengthening of the management of current health care to the

minimum requirements of the program in order to mimic the delay in diagnosis and increase the initiation of treatment for confirmed cases of diseases for diagnostic screening with special look is needed in this research for phenylketonuria, seeking to develop strategies to improve the operation, promoting a greater agility in the whole process and the start of treatment occurs in adequate time.[21,22]

CONCLUSION

Studies have shown that treatment is significantly more effective when deployed in the preclinical phase of the disease, because of their minimum requirements and maintaining its efficiency applicable on a large scale and low cost.

It is inferred after analysis that the Newborn Screening Program is extremely relevant for screening and early treatment of children diagnosed with PKU, but this does not guarantee a cure, since genetic diseases deserve further studies and even with proper treatment still there is the presence of many losses in lives of children with phenylketonuria, especially in personal-social, language and adaptive fine motor areas. Thus, it is hoped through this study a contribution to scientific production and fostering new research related to this theme.

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